REMARKS

Claims 1, 2, 4, 5, 7, 9, 10, 12, 13, 15, 16, 19 and 22 are pending in the present application. By the present communication, claims 5, 13 and 19 have been amended. Applicants respectfully request entry of the amendments set forth in this response under 37 CFR §1.116. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Upon entry of the present amendment, claims 1, 2, 4, 5, 7, 9, 10, 12, 13, 15, 16, 19 and 22 will be pending.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 15, 16, 19 and 22 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, is respectfully traversed as moot in light of the claim amendments. Specifically, the Examiner alleges that the limitation "inflammation" in the last line of claim 15 is not clear because the term may either refer to vascular inflammation or neurological inflammation. Applicants have amended claim 15 to specify that neurological inflammation is reduced. Accordingly, Applicants respectfully submit that claim 15, and claims 16, 19 and 22 dependent therefrom meet the requirements of 35 U.S.C. §112, second paragraph, and request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 102(e)

The rejection of claims 1, 2, 4, 9, 10, 12, 15 and 22 under 35 U.S.C. § 102(e) as being anticipated by Grinnell (U.S. Patent No. 6,268,337, hereinafter "Grinnell") is respectfully traversed. The Examiner alleges that the '337 patent teaches intravenous administration of activated protein C ("APC") to subjects with vascular occlusive and arterial thromboembolytic disorders (citing columns 3-4 and column 8, lines 28-33). Further, the Examiner states that claims 1-2, 4, 9-10, 12 and 15 recite the term "comprising" which is open-ended language that does not exclude additional, unrecited elements or method steps (MPEP § 2111.03).

Although Applicants concede that the claims at issue do recite open-ended language that does not exclude additional, unrecited elements or method steps, claim 1, as amended in the Response filed May 3, 2004, provides the limitation "...a *therapeutically effective amount* of activated protein C (APC) *in a bolus injection.*" As defined by the specification of the application at page 15, lines 20-22, the phrase "therapeutically effective" refers "to that amount of APC that is of sufficient quantity to ameliorate the cause or symptoms of the disease." Thus, although claim 1 may include additional, unrecited elements, the limitation "...a *therapeutically effective amount* of activated protein C (APC) *in a bolus injection,*" refers to a bolus injection containing the entire amount of APC that will ameliorate the cause or symptoms of the disease (*i.e.*, a therapeutically effective amount).

Grinnell, on the other hand, teaches that "the APC will be administered by injecting a *portion* of the appropriate dose per hour as a bolus injection over time from about 5 minutes to about 120 minutes, followed by continuous infusion...." (col. 4, line 66 – col. 5, line 4). Grinnell is silent with regard to providing the entirety of the APC dose in a single bolus injection to a subject. In fact, Grinnell describes intravenous administration of APC to a group of twelve dogs (Example 2), wherein the APC is administered in a *continuous intravenous infusion* of 2.0 mg/kg/hr APC for two hours, commencing 30 minutes after total vessel occlusion occurred. Further, Grinnell describes, at Example 1, the administration of APC to a group of six humans. As with Grinnell's dog study, *continuous infusion* of APC was performed. Accordingly, Grinnell '337 does not teach each and every element of the pending claims, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

Rejection under 35 U.S.C.§ 103(a)

The rejection of claims 1, 2, 4, 5, 7, 9, 10, 12, 13, 15, 19 and 22 under 35 U.S.C. § 103(a) as allegedly unpatentable over Grinnell et al. (U.S. Patent No. 6,268,337) in view of Arnljots and Hickenbottom is respectfully traversed. The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent

Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of

hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The Examiner alleges that Grinnell teaches the bolus or intravenous administration of activated protein C (APC) to subjects with vascular occlusive and arterial thromboembolytic disorders, including stroke. As discussed above, Grinnell is silent with regard to the administration of a therapeutically effective amount of APC in a bolus injection, as required by Applicants' invention.

Applicant respectfully submits that Arnljots does not cure the deficiencies of Grinnell. Arnljots teaches that the anti-coagulant action of APC is enhanced by the nonenzymatic cofactor, Protein S. Although Arnljots teaches that the substances are administered in a bolus injection, Arnljots discloses that protein S is administered in concentrations of 0.5, 0.1, or 0.05 mg/kg (page 938, col. 2, paragraph 2). Further Arnljots concluded that "Bovine APC (0.1 mg/kg), when given together with an approximately equimolar amount of bovine protein S (0.1 mg/kg), produced a powerful antithrombotic response...." (p. 938, col. 2, paragraph 5). However, Arnljots is silent with regard to concentrations of protein S that are greater than 0.5 mg/kg. In fact, one of skill in the art would be lead away from Applicants' invention because of the conclusion that APC should be administered in equimolar concentrations of protein S. Finally, Arnljots teaches away from the claimed invention by suggesting the need to combine Protein S with APC in order to achieve positive results. In contrast, the claimed invention describes not only the benefits of APC administered concurrently with protein S, but the positive neurological effects of APC alone. Applicants respectfully submit that there is no suggestion to combine the disclosures of Grinnell and Arnljots to arrive at Applicants' invention, and therefore there is no expectation that such a combination would be successful.

Applicant respectfully submits that Hickenbottom does not cure the deficiencies of Grinnell in view of Arnljots. Hickenbottom teaches that NMDA receptor antagonists and calcium channel antagonists are neuroprotective agents that are administered to acute stroke patients. As discussed above, the combined disclosures of Grinnell and Arnljots does not render Applicants' invention obvious. However, Hickenbottom does not describe the use of

APC, either alone or in conjunction with Protein S, as a neuroprotective agent. In fact, Hickenbottom is silent with regard to concentrations of any neuroprotective agents. It would not have been obvious, taking the disclosure of the art cited with regard to the effects of APC treatment on thromboembolism, in combination with Hickenbottom's discussion of possible neuroprotective agents for combating the negative effects of ischemia, to consider and then examine the possibility of using APC as a neuroprotective agent. Applicants respectfully submit that there is no suggestion to combine the disclosures of Grinnell, Arnljots and Hickenbottom to arrive at Applicants' invention, and therefore there is no expectation that such a combination would be successful.

Accordingly, it is respectfully submitted that the Examiner has not met the burden of proving *prima facie* obviousness under 35 U.S.C. § 103(a), and withdrawal of the rejection is respectfully requested.

Claim 16 is also rejected under 35 U.S.C. § 103(a) as anticipated by Grinnell '337, Arnljots, and Hickenbottom as applied to claims 1-2, 4-5, 7, 9-10, 12-13, 15, and 19 in further view of Grinnell '514. Claim 16 depends from any of claims 1, 9, or 15, and further provides the administration of an anticoagulant, an anti-platelet, and/or a thrombolytic agent. For the reasons discussed above, claims 1, 9, and 15 are not obvious in view of Grinnell '337, Arnljots, and Hickentbottom. Similarly, the claims are not obvious when taken in further view of Grinnell '514.

Grinnell '514 allegedly teaches the intravenous administration of activated protein C (APC) to subjects with thrombotic disorders (including, but not limited to, stroke, venous thrombosis, myocardial infarction, unstable angina, etc.). Applicant submits that while attacking references individually is impermissible where the rejections are based on combinations of references, it remains necessary that "the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicant asserts that the combined references of Grinnell

'337, Arnljots, Hickenbottom, in further view of Grinnell '514, do not teach all of the claimed limitations. Specifically, all of the references are silent with regard to concentrations of protein S that are greater than 0.5 mg/kg, as is required by amended claim 16. In fact, one of skill in the art would be lead away from Applicants' invention because of the conclusion that APC should be administered in equimolar concentrations of protein S.

Accordingly, it is respectfully submitted that the Examiner has not met the burden of proving *prima facie* obviousness under 35 U.S.C. § 103(a), and withdrawal of the rejection is respectfully requested.

Finally, claims 15-16, 19 and 22 are rejected under 35 U.S.C. § 103(a) as being allegedly anticipated by Griffin (U.S. Patent No. 5,084,274; hereinafter "Griffin '274") (our inventors are Griffin and Zlokovic) in view of Arnljots. The Examiner alleges that Griffin '274 teaches the intravenous administration of APC to subjects with arterial thrombotic occlusion or thromboembolism (citing column 3, lines 8-19 and columns 5-8). It is further alleged that Griffin '274 discloses that APC may be administered alone or in combination with a thrombolytic agent (citing column 2, lines 9-20). However, Griffin '274 teaches that "[t]he APC was given by injection one-fourth to one-third of the total PC dose as a bolus and the remaining three-fourths to two-thirds of the does as continuous infusion for one hour." (see col. 3, lines 9-12). Griffin '274 is silent with regard to protein S.

As stated above, Arnljots teaches that the anti-coagulant action of APC is enhanced by the nonenzymatic cofactor, Protein S. Although Arnljots teaches that the substances are administered in a bolus injection, Arnljots discloses that protein S is administered in concentrations of 0.5, 0.1, or 0.05 mg/kg (page 938, col. 2, paragraph 2). Further, Arnljots concluded that "Bovine APC (0.1 mg/kg), when given together with an approximately equimolar amount of bovine protein S (0.1 mg/kg), produced a powerful antithrombotic response...." (p. 938, col. 2, paragraph 5). However, Arnljots is silent with regard to concentrations of protein S that are greater than 0.5 mg/kg. In fact, one of skill in the art would be lead away from Applicants' invention because of the conclusion that APC should be administered in equimolar concentrations of protein S. Therefore, the combined

references of Griffin '274 and Arnljots would not arrive at Applicant's invention, which requires a concentration of protein S of about 2 mg/kg. Finally, Arnljots teaches away from the claimed invention by suggesting the need to combine protein S with APC in order to achieve positive results. In contrast, the claimed invention describes not only the benefits of APC administered concurrently with protein S, but the positive neurological effects of APC alone. Applicants respectfully submit that there is no suggestion to combine the disclosures of Griffin '274 and Arnljots to arrive at Applicants' invention, and therefore there is no expectation that such a combination would be successful.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on claims 1, 2, 4, 5, 7, 9, 10, 12, 13, 15, 16, 19 and 22 is respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Enclosed is check No. 574394 in the amount of $60.00 for One Month Extension of Time fee. However, the Commissioner is hereby authorized to charge any additional fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NUMBER 28213